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(54) Title: PEPTIDES KETOAMIDES, KETOACIDS, AND KETOESTERS

(57) Abstract

Peptides ketoamides, ketoacids, and ketoesters, their use in inhibiting serine proteases and cysteine proteases.

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527.62; C, 63.74; H, 7.07; N, 7.96. Found: C, 63.66; H, 7.09; N, 7.92. NMR ($CDCl_3$) ok. MS (FAB) m/e = 528.8 (M+1).

Example 65

Z-Leu-Abu-CONH-CH_2-C_4H_4N. This compound was synthesized from the corresponding protected α-ketoester and 4-(aminomethyl)pyridine in 45 % yield by the procedure described in Example 59. The product was greenish yellow solid. Single spot on TLC, R_f = 0.55 ($CHCl_3$/CH_3OH 10:1); mp 124-126 °C. Anal: calcd. for $C_{25}H_{32}N_4O_5$: 468.55; C, 64.08; H, 6.88; N, 11.96. Found: C, 63.88; H, 6.87; N, 11.96. NMR ($CDCl_3$) ok. MS (FAB) m/e =469 (M+1).

It is obvious that those skilled in the art may make modifications to the invention without departing from the spirit of the invention or the scope of the subjoined claims and their equivalents.

Table I. Inhibition of serine proteases by peptide ketoesters and ketoacids.[a]

Compounds	K_I (μM)			
	HLE	PPE	Cathepin G	Chymotrypsin
Bz-DL-Phe-COOEt			58	0.28
Bz-DL-Ala-COOEt	640	590		
Bz-DL-Ala-COOH	3100	3200		
Bz-DL-Ala-COOBzl	19	23		
Bz-DL-Ala-COO-*n*-Bu	260	NI[b]		
Bz-DL-Ala-$COOCH_2$-C_6H_4-CF_3 (para)	81[c]	11[c]		
Z-Ala-DL-Ala-COOEt	100	210		
Z-Ala-DL-Ala-COO-*n*-Bu	250	80		
Z-Ala-DL-Ala-COOBzl	46	11		
MeO-Suc-Ala-DL-Ala-COOMe	470[c]	520[c]		
Z-Ala-Ala-DL-Ala-COOEt	1.3	0.65		
Z-Ala-Ala-DL-Nva-COOEt	0.52	0.36		
Z-Ala-Pro-DL-Ala-COOEt	2.8	2.4		
Z-Ala-Ala-DL-Abu-COOEt	0.12	0.15		
Z-Ala-Ala-DL-Abu-COOBzl	0.09	0.08		
Z-Ala-Ala-DL-Abu-$COOCH_2$-C_6H_4-CF_3 (para)	0.08	0.33		
MeO-Suc-Val-Pro-DL-Phe-COOMe			1.1	0.26
Z-Ala-Ala-Ala-DL-Ala-COOEt	0.3	0.14		
MeO-Suc-Ala-Ala-Pro-DL-Abu-COOMe	0.42	0.93		

[a]Inhibition constants were measured in 0.1 M Hepes, 0.5 M NaCl, pH 7.5 buffer, 9 % Me_2SO and at 25 °C.

[b]No inhibition.

[c]Noncompetitive inhibition.

Table II. Inhibition of serine proteases by peptide ketoesters and ketoacids.[a]

Compounds	K_I (μM)					
	Bovine Trypsin	Bovine Thrombin	Human Plasma Kallikrein	Porcine Pancreatic Kallikrein	Human Factor XIa	Human Plasmin
Bz-Dl.-Arg COOEt	58[b]	48[b]	>240	>240	38[c]	14[b]
Bz-DL-Lys-COOEt	1.6[d]	>240	76[b]	>140	140[b]	
Bz-DL-Lys-COOEt	4.1[d]	31	120	>140		
H-Gly-Dl.-Lys-COOEt	2.8[d]		>240	NI[e]		
H-Ala-DL-Lys-COOEt	3.4[d]		>270	>270		
H-Pro-Dl.-Lys-COOEt	17[d]		>120	NI		
H-Phe-Dl.-Lys-COOEt	16[d]		>180	>140		
H-Leu-Ala-Dl.-Lys-COOEt						

[a]Inhibition constants were measured in 0.1 M Hepes, 10 mM $CaCl_2$, pH 7.5 buffer, 5.6-8.8 % Me_2SO and at 25 °C. Z-Arg-SBzl or Z-Gly-Arg-SBu-i were used as substrates.

[b]Competitive inhibition.

[c]Uncompetitive inhibition.

[d]Enzyme and inhibitor was preincubated before addition of the substrate.

[e]No inhibition at 120-240 μM.

Table III. Inhibition of cysteine proteases by peptide ketoesters and ketoacids.

Compounds	K_I (μM)			
	Papain[a]	Cathepsin B[b]	Calpain I[c]	Calpain II[c]
Z-Leu-Abu-COOEt			0.04	0.4
Z-Leu-Phe-COOEt			0.23	0.4
Z-Leu-Nle-COOEt			0.12	0.18
Bz-DL-Phe-COOEt	500[d]	64		
Z-Phe-DL-Phe-COOEt	1.8	0.1		
Z-Phe-DL-Ala-COOEt	3.6	3.2		
Z-Ala-Ala-DL-Ala-COOEt	1.5	2.2	200	
Z-Ala-Ala-DL-Abu-COOEt	0.9	10	50	200
Z-Ala-Ala-DL-Abu-COOBzl	30	60		
Z-Ala-Ala-DL-Nva-COOEt	30	0.1		
Z-Ala-Pro-DL-Ala-COOEt	26	66		
MeO-Suc-Val-Pro-DL-Phe-COOMe	1.1	0.1		
	2.9[d]			
Z-Ala-Ala-Ala-DL-Ala-COOEt	2.1	10.0		
MeO-Suc-Ala-Ala-Pro-Abu-COOMe	0.7	6.0	100	

[a]Inhibition constants were measured in 0.05 M Tris·HCl, pH 7.5 buffer , containing 2 mM EDTA, 5 mM cysteine (freshly prepared), 1 % Me_2SO, and at 25 °C. N^{α}-Benzoyl-Arg-AMC was used as a substrate.

[b]Inhibition constants were measured in 88 mM KH_2PO4, 12 mM Na_2HPO4, pH 6.0 buffer , containing 1.33 mM EDTA, 2.7 mM cysteine (freshly prepared), and at 25 °C. Z-Arg-Arg-AFC was used as a substrate.

[c]Inhibition constants were measured in 20 mM Hepes, pH 7.2 buffer , containing 10 mM $CaCl_2$, 10 mM β-mercaptoethanol, and at 25 °C. Suc-Leu-Tyr-AMC was used as a substrate.

[d]Inhibition constants were measured in 50 mM Tris·HCl, pH 7.5 buffer , containing 20 mM EDTA, 5 mM cysteine, 9 % Me_2SO, and at 25 °C. N^{α}-Benzoyl-Arg-NA was used as a substrate.

Table IV. Inhibition of Calpain I, Calpain II, Cathepsin B, PP Elastase, Papain, Platelets by Peptide Ketoamides, Ketoesters, and Ketoacids. Stability in Plasma and in Liver.

Inhibitor	K_I (uM)							t1/2 plasma	t1/2 liver
	Calpain I	Calpain II	CathB	Chym	elastase	papain	platelet		
Z-Leu-Abu-COOEt	4.5	0.4	30	>100	>100	220	42	2.8	
Z-Leu-Abu-COOnBu	1.8		4	>100	25	10	28		
Z-Leu-Abu-COOBz	9.5	0.47	4	40	>100	40	++		
Z-Leu-Leu-Abu-COOEt	1.8	2.6	22	>100	25		40		
2-NapSO2-Leu-Leu-Abu-COOEt	16	1.4	25	35	47		100	>60	
2-NapCO-Leu-Leu-Abu-COOEt		0.09		>300	28			25	
Tos-Leu-Leu-Abu-COOEt	33		69	25	28		30	30	
Ph-(CH2)2-CO-Leu-Abu-COOEt		1.2							
Ph-(CH2)3-CO-Leu-Abu-COOEt									
Z-Leu-Abu-COOH	0.075	0.022	1.5	>150	>150		8	>60	>60
Z-Leu-Abu-CONHEt	0.5	0.23	2.4	>150	65		1.5	>60	>60
Z-Leu-Abu-CONHnPr		0.25	8	>300	2		70	>60	>60
Z-Leu-Abu CONHnBu	0.2		13	>300	5		2.0	>60	>60
Z-Leu-Abu-CONHiBu		0.14	4	>300	40		28	>60	
Z-Leu-Abu-CONHBz		0.35	2	>300			1.5	>60	>60
Z-Leu-Abu-CONH-(CH2)2-Ph		0.022							
Z-Leu-Abu-CONH-(CH2)3-Mpl		0.041							
Z-Leu-Abu-CONH-(CH2)7CH3		0.019							
Z-Leu-Abu-CONH-(CH2)17CH3									
Z-Leu-Abu-CONH-(CH2)2OH		0.078							

Table IV (Continued). Inhibition of Calpain I, Calpain II, Cathepsin B, PP Elastase, Papain, Platelets by Peptide Ketoamides, Ketoesters, and Ketoacids. Stability in Plasma and in Liver.

Inhibitor	K_I (uM)								
	Calpain I	Calpain II	CathB	Chym	elastase	papain	platelet	t1/2	t1/2
Z-Leu-Abu-CONH-$(CH_2)_2O(CH_2)_2OH$	0.16								
Z-Leu-Phe-COOEt	1.8	0.4	340	0.05	>100	75	42	7.8	
Z-Leu-Phe-COOnBu	5.0	1.1	15	0.15	>100	15	+++	7.7	
Z-Leu-Phe-COOBz	3.4	1.6	45	1.6	>100	45	++	1.9	
Z-Leu-Leu-Phe-COOEt	1.4	1.9	42	0.26	>100	15	++		
Z-Leu-Phe-COOH	0.0085	0.0057	4.5	76	>150		6.5	>60	>60
Z-Leu-Phe-CONHEt	7.0	0.32	6	73	>150		1.7	>60	>60
Z-Leu-Phe-CONHnPr	15.0	0.05	3	18	>300		24	>60	>60
Z-Leu-Phe-CONHnBu		0.028	3	8	>100		38	>60	>60
Z-Leu-Phe-CONHiBu		0.065	4	24			22	>60	
Z-Leu-Phe-CONHBz		0.046							
Z-Leu-Phe-CONH$(CH_2)_2$Ph		0.024		(2)			3.0	>60	
Z-Leu-Nle-COOEt		0.18	20		2.2	190	20	3.7	
Z-Leu-Nva-COOEt	1.4	1.2	25	160	2.3	150	40	2.8	
Z-Leu-Met-COOEt	1.0	1.5	55	1.75	>100	140	+	8	
Z-Leu-4-Cl Phe-COOEt	<4.0	0.4	50	0.9	>100	150	+		

(+++ = excellent activity; ++ = good activity, + = moderate activity; quantitiative measurements not yet complete)

What is claimed is:

1. A compound of the formula:

M_1-AA-NH-CHR_2-CO-CO-NR_3R_4

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_2 is selected from the group consisting of C_{1-8} branched and unbranched alkyl, C_{1-8} branched and unbranched cyclized alkyl, and C_{1-8} branched and unbranched fluoroalkyl;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an

attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

2. A compound of the formula:

$$M_1\text{-}AA_2\text{-}AA_1\text{-}CO\text{-}NR_3R_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, C_1-C_{10} acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA_1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-

cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

AA_2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

3. A compound of the formula:

M_1-AA-AA-AA-CO-NR_3R_4

or a pharmaceutically acceptable salt, wherein

M_1 represents H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;

X is selected from the group consisting of C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluorenyl, phenyl, phenyl substituted with K, phenyl disubstituted with K, phenyl trisubstituted with K, naphthyl, naphthyl substituted with K, naphthyl disubstituted with K, naphthyl trisubstituted with K, C_{1-10} alkyl with an attached phenyl group, C_{1-10} alkyl with two attached phenyl groups, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached

phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, and C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

J is selected from the group consisting of halogen, COOH, OH, CN, NO_2, NH_2, C_{1-10} alkoxy, C_{1-10} alkylamine, C_{2-12} dialkylamine, C_{1-10} alkyl-O-CO-, C_{1-10} alkyl-O-CO-NH-, and C_{1-10} alkyl-S-;

K is selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkoxy, NO_2, CN, OH, CO_2H, amino, C_{1-10} alkylamino, C_{2-12} dialkylamino, $C_{1-C_{10}}$ acyl, and C_{1-10} alkoxy-CO-, and C_{1-10} alkyl-S-;

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the α-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH_2-CH(CH_2CHEt_2)-COOH, alpha-aminoheptanoic acid, NH_2-CH(CH_2-1-napthyl)-COOH, NH_2-CH(CH_2-2-napthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

R_3 and R_4 are selected independently from the group consisting of H, C_{1-20} alkyl, C_{1-20} cyclized alkyl, C_{1-20} alkyl with a phenyl group attached to the C_{1-20} alkyl, C_{1-20} cyclized alkyl with an attached phenyl group, C_{1-20} alkyl with an attached phenyl group substituted with K, C_{1-20} alkyl with an attached phenyl group disubstituted with K, C_{1-20} alkyl with an attached phenyl group trisubstituted with K, C_{1-20} cyclized alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with a morpholine [-N(CH_2CH_2)O] ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a piperidine ring attached through nitrogen to the alkyl, C_{1-10} alkyl with a pyrrolidine ring attached through nitrogen to the alkyl, C_{1-20} alkyl with an OH group attached to the alkyl, -$CH_2CH_2OCH_2CH_2OH$, C_{1-10} with an attached 4-pyridyl group, C_{1-10} with an attached 3-pyridyl group, C_{1-10} with an attached 2-pyridyl group, C_{1-10} with an attached cyclohexyl group, -NH-CH_2CH_2-(4-hydroxyphenyl), and -NH-CH_2CH_2-(3-indolyl).

4. A compound of the formula:

$$M_1\text{-AA-AA-AA-AA-CO-NR}_3\text{R}_4$$

or a pharmaceutically acceptable salt, wherein

M_1 represents H. NH_2-CO-, NH_2-CS-, NH_2-SO_2-, X-NH-CO-, X_2N-CO-, X-NH-CS-, X_2N-CS-, X-NH-SO_2-, X_2N-SO_2-, X-CO-, X-CS-, X-SO_2-, X-O-CO-, or X-O-CS-;